IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Robert Lanza et al.

Application No.: 09/655,815 Group Art Unit: 1632

Filed: September 6, 2000 Examiner: THAIANN N. TON

For: METHOD FOR GENERATING IMMUNE-COMPATIBLE CELLS AND TISSUES USING NUCLEAR TRANSFER TECHNIQUE

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

On June 4, 2003, Appellant appealed to the Board of Patent Applications from the final rejection of claims 1-7 and 11-14. The following is Appellant's Appeal Brief submitted pursuant to 37 C.F.R. § 1.192.

STATUS OF CLAIMS

Claims 1-7 and 11-14 stand finally rejected. Prior claims 8-10 and 15-55 were cancelled to expedite protection. A copy of all of the pending, appealed claims 1-7 and 11-14 are attached as Appendix A.

RELATED CASES

There are no related cases on appeal or involved in interference.

REAL PARTY IN INTERESTS

The real party in interest to this appeal is Advanced Cell Technology, Inc. the sole assignee of this application.

STATUS OF AMENDMENTS

An amendment after final rejection was submitted on June 4, 2003, amending Claim 1, canceling then-rejected claims 38-48, and canceling non-elected claims 15-19, 29-32, 24-37 and 49-55. As indicated by Advisory Action mailed on July 1, 2003, this amendment was entered in its entirety.

SUMMARY OF THE INTERVENTION

The present invention, as evidenced by the claims on appeal, relates to methods for testing the immune compatibility of cloned cells or tissues in a non-human animal model comprising the following steps:

a) obtaining a cell from a donor animal;

b) removing the nuclear DNA from a recipient oocyte, and transferring the nucleus of said donor cell into the recipient oocyte under conditions that result in the generation of a non-human embryo; [underlined for emphasis]

c) isolating an embryo having at least one cell, an embryonic disc and/or stem cell from said non-human embryo;

d) injecting said embryo, disc and/or stem cell into a non-human donor animal at the same time as a control embryonic disc and/or stem cell; and

e) examining the injection sites for teratoma formation and signs of injection of the injected cells or of teratomas derived therefrom.

Essentially, therefore the present invention provides novel assays for predicting and ascertaining whether cloned cells and tissues become stably engrafted as evidenced by whether they exhibit signs of rejection. These assays solve an inherent problem in the art relating to the use of cloned cells and tissues for transplant because, as discussed in the application, cloned cells and tissues are not necessarily antigenically identical to the transplant recipient. For example, they lack the mitochondrial DNA of the donor cell and gain the mitochondrial DNA of the recipient enucleated oocyte used to produce the cloned embryo. Therefore, there is a concern whether such cells will be immune compatible upon transplantation into a donor animal. In other words, there is a possibility that they, dependent, e.g., on the antigenicity of the mitochondrial antigens expressed thereby, may be rejected by the transplant recipient. This may occur, e.g. because of an immune response to transplanted cells which contain and may express on their surface antigenic mitochondrial antigens. In this regard, as discussed at pages 4-5 of the application, it was known that mitochondrial peptides can be expressed on the surface of mammalian cells, and that mitochondrial peptides can elicit an immune injection response (e.g. cells may become susceptible to lysis by

immune cells, particularly cytotoxic T lymphocytes). See in particular, the discussion on page 4, lines 16-29 of the subject application wherein prior art references discussing immune responses to mitochondrial antigenic peptides are discussed).

Thus, the present invention alleviates a potential problem and concern in the context of selecting cloned cells and tissues that are appropriate and safe for allogeneic transplantation; specifically it provides a method of selecting cloned allogeneic cells and tissues which are stably maintained and do not elicit undesirable rejection responses which may promote graft instability and cause undesirable immune reactions in the host.

ISSUES ON APPEAL

Are claims 1-7 and 11-17 adequately described and enabled by the teachings of this application?

With respect to these issues, the only outstanding rejections are under §112 first paragraph. The Examiner has rejected all of the claims on two bases:

1) that the claims do not positively explicate an activation step and therefore are allegedly not adequately enabled or described; and

2) the specification allegedly does not provide "sufficient teaching or guidance" with respect to the means by which the immune compatibility of the cloned cells or teratoma containing the cloned cells is determined. Based thereon, these claims allegedly violate the

enablement and written description requirements of §112 first paragraph.

GROUPING OF CLAIMS

All of claims 1-7 and 11-14 stand or fall together as none of these claims positively recite an activation step and because all of the claims are submitted to be adequately enabled and described by the same teachings in the specification relating to the means whereby the sites of injection of transplanted cells are examined for "signs of rejection".

ARGUMENT

I. Appellants' Claims Are Sufficiently Enabled and Described By The Specification Because One Skilled in the Art Would Readily Comprehend That "Conditions that Result in the Generation of a Non-Human Embryo" Would Necessarily Include Conditions that Result in the Activation of the Embryo Such That is Capable of Giving Rise to Different Differentiated Cell Types, i.e., a Teratoma.

The claims on appeal expressly state that the injection sites [of cloned cells] are examined for "teratomas" which are defined in the application at page 5, lines 25-27, as being "a group of differentiated cells containing derivatives of mesoderm, endoderm, or ectoderm resulting from totipotent cells". Because of this terminology, the claims implicitly require that the NT embryo is activated.

By contrast, if activation of the nuclear transfer embryo did not occur, totipotent cells will not be obtained, i.e., cells which are capable of giving rise to all three cell lineages endoderm, ectoderm and mesoderm, i.e., a teratoma. Therefore, the claims implicitly require an activation step.

With further respect to the failure of the claims to positively recite an activation step, it is not necessary that this be stated expressly as it was well known at the time of the invention that effective nuclear transfer cloning procedures, i.e., procedures which result in embryos that give rise to different differentiated cell types necessarily include conditions that "activate" the embryo. In fact, as evidence of this fact and as argued during prosecution of this application, the present patent application incorporates by reference a published patent that describes nuclear transfer cloning procedures which were well known in the art at the time of invention, and which included activation procedures. Particularly, this application incorporates by reference in its entirety to Stice, US Patent 5,945,577. Applicant note that this patent is exclusively licensed to the present assignee, and as explained to the Examiner during prosecution contains substantial written description establishing the well known fact that nucleic transfer cloning methods inherently include activation means. This incorporation by reference establishes that the inclusion of such a means would have been routine and well known to the ordinary artisan at the time of invention. For example, as noted in the '577 patent disclosure, such well known methods include exposure of the NT fusion embryo to cool temperature conditions, application of electrical or chemical shock, treatment with ethanol, and treatment with divalent cations such as calcium. Thus, based on the state of the art, as evidenced by an issued United States patent 5,945,577 incorporated by reference in its entirety in this application, it would be abundantly clear that the recitation or "conditions that result in the generation of a non-human

embryo" would necessarily be understood by a skilled artisan to include some means that "provide for activation of the embryo."

In fact, at the time of the invention, and as further argued during prosecution of these present application, it was also well known at the time of the invention that oocytes, if sufficiently mature, spontaneously activate unless conditions are taken to preclude activation, e.g. by maintaining oocytes in a culture medium lacking calcium. (Appellant notes that the Stice '577 patent incorporated by reference discloses that increasing divalent cations such as calcium is a well known means of effecting embryo activation). Thus, Appellants maintain that the appealed claims would be clearly understood, based on the teachings of the application and the state of the art, relating to nuclear transfer cloning methods, to include conditions necessary for formation of a viable embryo, i.e., one that gives rise to different differentiated cell types, e.g., by the use of culture conditions that allow for activation of the NT embryo to proceed.

Appellant also respectfully submits that the '577 patent that is incorporated by reference in its entirety further establishes that the claims are enabled and are sufficiently described based on the fact that numerous effective nuclear transfer embryo activation methods were well known at the time of the invention. Therefore, a skilled artisan would readily know both that an effective process for producing NT embryos would include conditions known to favor embryo activation, and would further know how to select such conditions.

Therefore, in summary, those skilled in the art would readily understand that the cloned methods, which include conditions for producing a NT embryo that gives rise to a teratoma would necessarily require that the process for producing the embryo be effected under conditions which were routine and well known at the time of the invention to induce embryo activation and differentiation.

2. Appellants' Specification Makes Adequately Clear How to Detect Signs of Rejection [of the Transplanted Cloned Cells in Treatment Resulting Therefrom].

The Examiner has maintained that the claims are not adequately described or enabled by the as-filed specification because it allegedly would be unclear what is intended by examining injection sites for "signs of rejection of the injected cells or of teratomas derived therefrom." However, the Examiner's rejection should be reversed because one skilled in the art, in possession of the specification, would readily understand what is intended by a means of evaluating whether the cloned tissues exhibit signs of rejection, and would be able to screen for such signs of rejection.

More specifically, the rejection should be withdrawn because the application describes and enables several means for evaluating whether an immune (rejection) response against implanted cells and teratomas is elicited and further discloses and enables that these detection means correlate to rejection responses.

Particularly, at page 8, lines 12-24, the application indicates that immune responses can be detected by assaying for antibodies, mitochondrial antigens and

lymphocytes specific for mitochondrial antigens as these antibodies and cytotoxic cells may result in "immune recognition and possibly graft rejection".

Thus, the application clearly describes that anti-mitochondrial antigen antibodies and cytotoxic T lymphocyte responses are indicative of immune responses against the implanted cells or treat teratoma.

Similarly, at page 12, lines 6-11, the as-filed application describes that "different animal" stem cells survive "better or longer depending on the cytotoxic T response or other immune reaction to foreign mitochondrial peptides." Quite clearly, it would be understood by a skilled artisan that increased survival means that the measured cytotoxic T lymphocyte (CTL) correlates to tissue rejection based on reduced tissue survival. Therefore, the application describes that screening for a CTL reaction is a suitable means of evaluating whether the host elicits a rejection response against the engrafted cloned cells.

Still further, at page 23, in an example, evaluating the stability of transplanted cloned cells in an animal model according to the invention, the application exemplifies the use of mitochondrial antibodies [anti – CD6 antibodies] to detect immune T and B cells [see page 23, lines 26-28", and further describes at page 24 that a histological comparison of control and cloned tissues indicated "a statistically significant ($p < 0.05$, student's t-test) increase in lymphocyte infiltration of the control implants/constructs (non-cloned) verses the cloned tissue types", (see page 27, lines 7-15 of the application) and that the data suggested that "the control

grafts were undergoing early graft rejection". Also, the application further indicates that "higher number of inflammatory cells were present throughout the control allgenetic scaffolds". (See page 27, lines 9-10).

Thus, the specification further describes and enables another method of evaluating whether there is a rejection response against implanted cloned tissues,, i.e., by screening for inflammatory cells, and thereby assessing whether rejection responses against transplanted cloned cells and tissues are manifested.

Based on the foregoing, Appellant maintains that the specification both adequately describes and enables various sustainable means for evaluating whether an animal engrafted with cloned cells exhibits signs of rejection and further establishes that these means correlate to rejection responses. Particularly, these disclosed means of detecting rejection include detecting increased number of immune cells versus an appropriate control, detecting of increased inflammatory cells at site of injection of cloned cells relative to approach control, detecting for an increased antibodies against mitochondrial antigens relating to controls, and the detection of cytotoxic T lymphocytes which elicit responses against transplanted cells. It would be clear based on the as-filed disclosure that any or all of these methods can be used in the claimed methods to detect whether there are "signs of rejection" to the injected cells or teratomas resulting therefrom.

CONCLUSION

In view of the above, Claims 1-17 and 11-14 are adequately described and enabled by the teachings of the application because:

(1) it would be understood by an ordinary skilled artison, especially based on the incorporation by reference to US Patent 5,945,577 that the conditions to produce a nuclear transfer embryo would include conditions that favor embryo activation otherwise embryos capable of giving rise to different differentiated cell types (teratomas) will not be obtained; and

(2) the specification enables and describes a variety of different means that would readily facilitate a skilled artisan to evaluate whether cloned cells or tissues exhibit "signs of rejection" vis-à-vis control cells or tissues, as recited in the claimed methods.

Therefore, the Examiner's §112 first paragraph rejection of Claims 1-7 and 11-14 should be reversed and this application be permitted to proceed to grant.

This Appeal Brief is accompanied by a check in the amount of the required appeal fee and 3-month extension of time fee. This amount is believed to be current, however, the Commission is hereby authorized to change any deficiency, or

credit any art program, to Deposit Account No. 05-1323.

A triplicate copy of this Appeal Brief is attached.

Respectfully submitted,

Date: October 23, 2003

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RLT:mld